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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,866	05/11/2005	Shishan Ji	P06927USO	8507

22885 7590 07/07/2010

MCKEE, VOORHEES & SEASE, P.L.C.
801 GRAND AVENUE
SUITE 3200
DES MOINES, IA 50309-2721

EXAMINER	
ALAWADI, SARAH	

ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
07/07/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patatty@ipmvs.com

Office Action Summary	Application No.	Applicant(s)	
	10/508,866	JI ET AL.	
	Examiner	Art Unit	
	SARAH AL-AWADI	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *2-6,14-32 and 37-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-13 and 33-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/06/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

INFORMATION DISCLOSURE STATEMENT

The IDS filed on 06/01/2010 is acknowledged.

RESPONSE TO RESTRICTION REQUIREMENT

Applicant's election without traverse of Group VI claims 1, 7-13 and 33-36 with the species of ester and polyethylene glycol in the reply filed on 06/01/2010 is acknowledged.

Claims 2-6, 14-32 and 37-60 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/01/2010.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1, 7-13 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Li et al. United States Patent 5,977,163, Santi et al., United States Patent 6,872,715, and Greenwald et al., Effective Drug Delivery by PEGylated Drug Conjugates as evidenced by Rhee et al. United States Patent 5,510,121.

Santi et al. teach conjugating various compounds including flavone compounds to a hydrophilic polymer such as polyethylene glycol (PEG), see column 29, lines 20-33 and table 2, column 24. The polymers (including PEG) that the compounds are conjugated to enhance aqueous solubility, see column 29, lines 20-33. The polymers of Santi are conjugated via an ester linkage to one or more hydroxyls of drugs including geldanamycin, see column 29, lines 31-33. The compositions of Santi are formulations of one or more active drugs and a pharmaceutically acceptable carrier. The composition may be in any suitable form such as solid, semisolid or liquid, and may include tablets and capsules, see column 27, lines 65-67 and column 28, lines 11-21.

Santi et al. does not expressly teach ester linkage groups with flavone compounds.

Li et al. teach drug polymer conjugates to polyethylene glycol of chemotherapeutic and antiangiogenic drugs which are linked through an ester, see column 2 lines 39-43 and column 4, lines 19-39. The ester is used to ensure that the active drug is released from the polymeric carrier. Li expressly states "when functional groups are used for drug conjugation, such as for example the hydroxyl of paclitaxel, a degradable linkage, an ester is used to ensure that the

active drug is released form the polymeric carrier" (polyethylene glycol), see column 4, lines 19-39.

It would have been prima facie obvious to the skilled artisan to form polymer drug conjugates with the flavones of Santi via an ester linkage. One would have been motivated to do so in view of Li et al. which teach that ester linkages ensure the drug is released from the polymer carrier. One would have been further motivated to use an ester linkages because it is taught in the art that when ester linkages are used for conjugation, the linkage is advantageous as it is more easily broken under physiological conditions allowing for sustained release of the conjugated agent, see Berg et al. column 12, lines 39-45 There would have been a reasonable expectation of success as Santi et al. teach polymer drug conjugations of specific compounds such as geldanamycin though ester linkages.

Neither Sanit nor Li teach the molecular weight of the PEG.

Greenwald et al. teach PEG conjugated to drugs, see abstract. The polyethylene glycols are advantageous to use for drug delivery as they are non-toxic and non-immunogenic, see page 218, introduction. Greenwald teaches that linkages could be chosen so that either pH or enzymatic degradation mediates prolonged drug release, see page 223, 1st paragraph. Greenwald further teaches designing different drugs by using ester linkages, see abstract and 3.1.1. and 3.1.2. Greenwald teach that esters employing PEG are especially effective linking groups in the design of drugs (prodrugs) since they aid in the rapid hydrolysis of the ester carbonyl bond and release drugs in a continuous effective manner, see page 223, section 3.1.1. Greenwald further teach that increasing the Mw of PEG increases the circulation lifetime ($t_{1/2}$) of the drug and prevents rapid renal excretion of the drug, see page 224.

It would have been prima facie obvious to the skilled artisan to conjugate polyethylene glycols with a weight between 300 to 60,000. One would have been motivated to do so because Greenwald teach that an increase in molecular weight (i.e between 6,000 and 50,000) increases the circulation lifetime of drugs. One would have been motivated to conjugate such PEG's to flavones in particular in order to increase the half life of the flavone compound. There would have been a reasonable expectation of success as Santi et al. teach the conjugation of compounds of the invention including flavones to PEG and it is exemplified in the art that conjugating drugs to PEG is a well known technique to increase the $t_{1/2}$ of drugs.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarah Al-Awadi whose telephone number is (571) 270-7678. The examiner can normally be reached on 9:30 am - 6:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bonnie Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated

information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARAH AL-AWADI/
Examiner, Art Unit 1619

/Shanon A. Foley/
Primary Examiner, Art Unit 1619